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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/728,173	12/01/2000	Keisuke Kuida		4567

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/728,173	KUIDA ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *02 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/01/2000*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction was received on 2/02/2005. Claims 1-7 are pending in the instant application. Applicant's election with traverse of group I drawn to a genetically altered animal defective in Caspase-9 in the reply filed on 2/02/2005 is acknowledged. Further, in a telephone interview on 3/10/05 applicant elected species a), drawn to the monoclonal antibody of unelected group III. Applicant argues that group I drawn to a genetically altered animal defective in Caspase-9 should be rejoined with group II, drawn to a method of making a genetically altered animal defective in Caspase-9 expression. Applicant's amendments and arguments have been fully considered and have been found persuasive in overcoming the grounds of restriction as applicable to groups I and II. Accordingly, groups I and II have been rejoined. However the restriction of group III is maintained for reasons of record. The new groups, in view of joining groups I and II, are group I-claims 1-5 and group II claims 6 and 7. The requirement is still deemed proper and is therefore made FINAL.

Claims 6 and 7 are withdrawn by the examiner from further consideration pursuant to 37 CFR 1.142(b).

Claims 1-5 are currently under examination.

Specification

The Specification is objected to because the Brief Description of the Drawings does not match the drawings submitted on 12/01/2000. Specifically, the Brief Description of the Drawings does not describe the panels and content of Figure 5. In fact there is no reference to Figure 5 at

all, see page 4 of the Specification. Figure 5 must be removed or the Brief Description of the Drawings must be amended. Further the Brief Description of the Drawings refers to Figure 7, however there is no figure 7 present in the drawings submitted on 12/01/2000. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 1 reads on a genetically altered animal defective in Caspase-9 expression. Said genetically altered animal defective encompasses a transgenic human. Claim 3 reads on a method of making a reads on a genetically altered animal defective in Caspase-9 expression. This method encompasses a method of making a transgenic human. While it is noted that the specification defines animals as all mammals, except human beings it is noted that the applicant cannot define words with meanings that are repugnant in the art. The term animal includes any mammal, fish, reptile, amphibian and bird. The claims are rejected since the broadest reasonable interpretation of the claims encompasses a method of making and a transgenic human.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1and 2 are drawn to a genetically altered animal defective in Caspase-9 expression. The claims encompass any animal that has been genetically altered in any way that causes defective caspase 9 expression. The claims encompass a genus of genetically altered animals that are defined solely by a defect in caspase 9 expression.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The claimed genus contemplated in the specification includes any animal deficient in or completely lacking caspase 9 expression (specification page 2). This encompasses caspase 9 knockout animals as well as animals with any genetic alterations that cause defective caspase 9 expression. The specification does not contemplate any specific genetic alterations in transcription factors or gene regulation that would lead to an increase or decrease in caspase 9 expression. The specification does not contemplate any specific animals with decreased or a total lack of caspase 9 expression, except caspase 9 constitutive knockout mice. A staggering number of different genetic alterations could potentially produce an animal with defective caspase 9 expression.

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional

characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the requirement that the animal have a genetic alteration that causes defective caspase 9 expression. Further the specification fails to identify any gene or sequence, common to all animals, other than caspase 9, which can be altered causing defective caspase 9 expression. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of any animal that has been genetically altered in any way that causes defective caspase 9 expression.

Claims 3-5 are drawn to a method of making a genetically altered animal defective in Caspase-9 expression. Claim 3 is drawn to providing any isolated DNA sequence comprising a genomic DNA sequence encoding caspase-9 with a deletion of the QACXG pentapeptide motif. However the specification does not disclose any other caspase-9 genomic DNA sequences other than the mouse sequence (example 1, pg. 8). The claims encompass a genus of caspase-9 genomic DNA sequences that are defined solely by the removal of the QACXG pentapeptide motif.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The claimed genus contemplated in the specification includes any caspase-9 genomic DNA sequences (specification page 5). This encompasses caspase-9 genomic DNA sequences from any mammal, bird, reptile, amphibian or fish. The specification does not contemplate any specific caspase-9 genomic DNA sequences other than the mouse caspase-9 genomic DNA sequence. While it is noted that the specification

contemplates screening genomic libraries to identify caspase 9 sequences in other species (Specification pg. 5), guidance on how to identify caspase-9 genomic DNA sequences is not considered to be evidence of possession. The number of different caspase-9 genomic DNA sequences that could potentially be isolated is equal to all of the different caspase-9 alleles present in all the animals in the world.

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the requirement that the different caspase-9 genomic DNA sequences lack the QACXG pentapeptide motif. Further the specification fails to identify any sequence, common to all animals, that could be used to identify caspase-9 genomic DNA sequence. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of any caspase-9 genomic DNA sequences.

The Revised Interim Guidelines state, "when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must

convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for any genetically altered animal defective in Caspase-9 expression or any caspase-9 genomic DNA sequences. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a caspase-9 knockout C57BL/6 mouse with a homozygous embryonic lethal phenotype, in which the endogenous caspase-9 gene is disrupted by the presence of a *neo* gene cassette that replaces the sequence encoding the pentapeptide motif (QACGG), wherein said endogenous caspase 9 gene does not produce a active caspase 9 protein, and a method of making the knockout mouse, wherein the *neo* gene cassette was integrated into the caspase-9 gene by homologous recombination and the transgenic C57BL/6 mouse strain is produced by embryonic stem (ES) cell chimeras, does not reasonably provide enablement for any genetically altered animal defective in caspase 9 expression or a method of making any such animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims encompass any genetic alteration in any animal that causes a defect in, caspase 9 expression. This includes animals that may have higher or lower levels of caspase 9 expression, since the term defective does not mean only a decrease. Therefore, the claims

encompass transgenic gain-of-function animals and animals with total or conditional gene knockouts of caspase 9, or any regulatory transcription factors as well as transgenic mice that express increased levels of negative regulatory factors, or dominant negative factors, or anti-sense RNA that inhibits caspase 9. The claims also encompasses a method of making a caspase 9 knockout in any animal by disrupting caspase-9 gene with the presence of a *neo* gene cassette that replaces the sequence encoding the pentapeptide motif (QACGG), wherein the *neo* gene cassette was integrated into the caspase-9 gene by homologous recombination and the and the transgenic mouse strain is produced by embryonic stem (ES) cell chimeras.

The state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammals comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that '[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without

general rules to obtain good expression of a transgene (page 275, column 1, lst paragraph; e.g., specific promoters, presence or absence of introns, etc.

Further, the claimed invention as filed would encompass making a transgenic mouse with a negative regulatory factors or dominant negative factors, or anti-sense RNA that inhibits caspase 9. However, the art of making a transgenic mouse is not predictable because of several factors. For example, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in non-targeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the "transgene" (see page 256, section 4 on transgene regulation and expression). Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing a caspase-9 transgene or dominant negative form of caspase 9 in one animal would have been functional in other animals and even if the promoter were active, or whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype.

The claims also encompass both constitutive and conditional caspase 9 knockout animals. However, the specification does not provide any guidance on how to make any conditional knockout animal. Leneuve et al. teaches that the presence of residual loxP sites after Cre

induced excision can lead to hypomorphic phenotypes {Leneuve et al. (2003) Nucleic Acids Research 31:1-8; pg. 1, col. 2}. While Leneuve et al. suggests that these remaining loxP sites can be partially removed using the tri-lox strategy, this method is not straightforward, because of variation in CRE-lox recombination between individuals and strong expression of EIIaCre in oocytes resulting in the excision of all floxed segments in these cells (pg. 1, col.2 to pg. 2 col. 2). Therefore the making of conditional knockouts remains unpredictable even in mice, which have one of the longest track records of being amendable for genetic manipulation of any species. Further, the specification does not disclose that any other part of the caspase 9 gene can be knocked out by homologous recombination and produce the same phenotype in any other mouse strain. Sanford et al. teaches that "the history of mouse genetics, which in itself can be termed the study of strain-dependent phenotype variability, tells us that as a backdrop to these approaches the genetic background onto which the targeted allele is placed can cause considerable variation in phenotype. This variation can present itself as completely different phenotypes, as variations in penetrance of phenotype, or as variable expressivity of phenotype." (Sanford et al. (201) Methods Mol. Biol. 158:217-25; Abstract). Strunk et al. agrees stating that analysis of different mouse strains indicates that different strains have different modifiers that function at different stages of development, which influences the timing of lethality due to homozygosity of a null allele {Strunk et al. (2004) Genetics 167:1821-1832; Abstract; pg. 1823, Fig. 1}. Given the lack of teachings in the specification on how to construct any transgenic animal defective in caspase-9 expression, the teachings in the art that making transgenic animal s is unpredictable and must be reduced to practice in order to reliably produce a specific phenotype, the teachings in the art that the successful construction of a specific phenotype with a transgene in one species of animal, is

not predictive of the odds of successfully constructing a transgenic animal of a different species with that same construct, the lack of guidance on making animals with conditional caspase 9 knockouts, and the lack of guidance that the phenotype of the caspase 9 knockout mouse can be duplicated in any other mouse strain, the skilled artisan would be unable to predict how to practice the invention as claimed, except as for making and using caspase-9 knockout C57BL/6 mouse with a homozygous embryonic lethal phenotype, in which the endogenous caspase-9 gene is disrupted by the presence of a *neo* gene cassette that replaces the sequence encoding the pentapeptide motif (QACGG), wherein said endogenous caspase 9 gene does not produce a active caspase 9 protein, and a method of making the knockout mouse, wherein the *neo* gene cassette was integrated into the caspase-9 gene by homologous recombination and the transgenic C57BL/6 mouse strain is produced by embryonic stem (ES) cell chimeras, without extensive and undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is vague because it reads on a pentapeptide motif wherein X is "arginine <u>of</u> glycine." It is unclear from the specification what is meant by the term "arginine <u>of</u> glycine." Therefore the metes and bounds of the claimed invention cannot be determined.

Please note that the closest prior art of record is exemplified by Hakem et al. {Hakem et al. (1998) Cell 94:339-352}, published on August 7, 1998, which teaches a caspase 9 knockout mouse and a method of making the mouse but was published two months after the priority date of 6/02/1998, of the application. Additional prior art of record is exemplified by Kuida et al. (Kuida et al. (1998) Cell 94 :325-37}, published on August 7, 1998, which teaches a caspase 9 knockout mouse and a method of making the mouse by the two con-inventors and additional co-authors but was published two months after the priority date of 6/02/1998, of the application.

No claims allowed

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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